

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2004/000166

## A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. <sup>7</sup>: C12Q 1/68 C12N 15/11 C12N 15/12 G06F 19/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

SEE ELECTRONIC DATABASES

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SEE ELECTRONIC DATABASES

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CaPlus, WPIDS (hepatocellular carcinoma, array or chip, differential, profile, gene expression, gene profile, microarray, DNA chip, gene chip, hepatocellular carcinogenesis), Medline (gene expression profiling/CT, oligonucleotide array sequence analysis/CT, protein array analysis/CT, carcinoma, hepatocellular/CT)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Smith, M.W. <i>et al.</i> 2003. Identification of novel tumor markers in hepatitis C virus-associated hepatocellular carcinoma. Cancer Research. 63:859-864. See whole document.	1-54
X	Li, Y. <i>et al.</i> 2003. DNA microarray analysis of gene expression profiles in hepatocellular carcinoma. Biochips. pp51-59. See whole document.	1-54
X	Chen, X. <i>et al.</i> 2002. Gene expression patterns in human liver cancers. Molecular Biology of the Cell. 13:1929-1939. See whole document. Note: This citation refers to supplemental information, including clone lists, provided on the authors' web site: <a href="http://genome-www.stanford.edu/hcc/supplement.shtml">http://genome-www.stanford.edu/hcc/supplement.shtml</a>	1-54



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search  
13 August 2004

Date of mailing of the international search report  
18 AUG 2004

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Li, Y. <i>et al.</i> 2002. Discovery and analysis of hepatocellular carcinoma genes using cDNA microarrays. <i>Journal of Cancer Research and Clinical Oncology</i> . 128:369-379. See whole document.	1-54
X	Okabe, H. <i>et al.</i> 2001. Genome-wide analysis of gene expression in human hepatocellular carcinomas using cDNA microarray: Identification of genes involved in viral carcinogenesis and tumor progression. <i>Cancer Research</i> . 61:2129-2137. See whole document.	1-54
X	Graveel, C.R. <i>et al.</i> 2001. Expression profiling and identification of novel genes in hepatocellular carcinomas. <i>Oncogene</i> . 20:2704-2712. See whole document.	1-54
X	Tackels-Horne, D. <i>et al.</i> 2001. Identification of differentially expressed genes in hepatocellular carcinoma and metastatic liver tumors by oligonucleotide expression profiling. <i>Cancer</i> . 92(2):395-405. See whole document.	1-54
X	Xu, X-R, <i>et al.</i> 2001. Insight into hepatocellular carcinogenesis at transcriptome level by comparing gene expression profiles of hepatocellular carcinoma with profiles of hepatocellular carcinoma with those of corresponding nincancerous liver. <i>Proceedings of the National Academy of Sciences (USA)</i> . 98(26):15089-15094. See whole document. Note: this citation refers to Tables 4-6 and Figure 3 displayed as supplemental information with the electronic copy of the citation on the PNAS website: <a href="http://www.pnas.org/cgi/content/full/98/26/15089/DC1">http://www.pnas.org/cgi/content/full/98/26/15089/DC1</a>	1-54

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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

The international application does not relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. The requirement of unity of invention under Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" relates to those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

This application is directed to the identification of marker genes indicative of hepatocellular carcinoma (HCC) that can be used to determine the presence or absence of HCC cells or tissues. However this concept is not new. See for example:

a) Graveel, C.R. *et al.* 2001. Expression profiling and identification of novel genes in hepatocellular carcinomas. *Oncogene*. 20:2704-2712.

(Continued on supplemental sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

**Continuation of Box No: III (Unity)**

b) Tackels-Horne, D. *et al.* 2001. Identification of differentially expressed genes in hepatocellular carcinoma and metastatic liver tumors by oligonucleotide expression profiling. *Cancer*. 92(2):395-405.

c) Okabe, H. *et al.* 2001. Genome-wide analysis of gene expression in human hepatocellular carcinomas using cDNA microarray: Identification of genes involved in viral carcinogenesis and tumor progression. *Cancer Research*. 61:2129-2137.

Each of these citations disclose the identification of 2 or more markers that are indicative of HCC.

Thus while a common feature of the applicant's markers may be that they are present in HCC tissue and not normal liver tissue, this is not considered a special technical feature as markers with such properties are well known in the art (see above documents).

Thus there does not appear to be a special technical feature common to all markers identified in the specification. Thus it would appear that the special technical features of the specification relate to the use of the sets of markers identified in each of Tables 1-4, ie the use of all the markers in either Table 1, 2, 3 or 4 for the identification of HCC with predictive accuracy. Further there does not appear to be a special technical feature common to all four sets of markers as they contain different numbers of markers, hence the application is directed to four (4) inventions as follows:

- 1) The markers identified in Table 1 when used to determine the presence or absence of HCC cells or tissues.
- 2) The markers identified in Table 2 when used to determine the presence or absence of HCC cells or tissues.
- 3) The markers identified in Table 3 when used to determine the presence or absence of HCC cells or tissues.
- 4) The markers identified in Table 4 when used to determine the presence or absence of HCC cells or tissues.

The ISA has chosen not to ask for additional fees as all four inventions can be covered by the one search statement relating to the identification and use of molecular markers able to determine the presence or absence of HCC.